DESIGN OF A NOVEL CONTINUOUS FLOW REACTOR FOR LOW PH VIRAL INACTIVATION

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Currently the Biopharamaceutical industry is moving from operating in batch mode to continuous manufacturing. Low pH viral inactivation is a highly effective and a common method used in monoclonal antibody purification processes. During this unit operation the product is pooled and held, presenting a major bottle neck to end-to-end continuous downstream processing. Moving from a holding tank to a tubular reactor would provide for a means of processing materials continuously. The major challenges with tubular reactors for this application include limiting and characterizing the axial dispersion to ensure sufficient incubation time. The main objective of this work was to design and characterization of the residence time distribution (RTD), exit age of fluid elements leaving the reactor, of a continuous tubular reactor (CTR) for low pH viral inactivation.

The following CTR design criteria were generated to streamline integration into the downstream purification process: (1) a ≤ 5 psi pressure drop along the length of the tube, (2) radial mixing within the reactor without moving parts to minimize axial dispersion, (3) a minimum residence time (MRT) approach was used to ensure that the desired product holding time was met, (4) operating at the laminar flow regime to limit shear on the product and minimize the pressure drop along the tube length while operating at flow rates sufficient for a 100 L bioreactor continuous process.

Curved pipes offer improved radial mixing due to the formation of Dean Vortices via centrifugal forces. Thus, to reduce axial dispersion, the reactor as designed to include curvature in flow path via alternating 270 turns which also induced changes in the flow direction with each turn or flow inversions. A modular design with incubation chambers that can be connected in series was generated and evaluated using computation fluid dynamic (CFD) simulation before a final design was 3D printed and experimentally evaluated. Comprehensive computational fluid dynamics modeling in ANSYS Fluent of the CTR via velocity profile and secondary flow streamlines show enhanced radial mixing due to secondary flows and changes in flow direction. CFD simulation results were validated by pulsed tracer experiments and were in sufficient agreement, RTD variance values within 6.7%, with the computational model. Scaling the CTR with length to ~115.1 m at 50 ml/min, resulted in a MRT of 70.4 ± 0.46 mins with a pressure drop of ~0.7 psi. With increased length the dimensionless RTD profiles become more symmetrical and tighter about the mean residence time, indicating a smaller deviation from plug flow with increased length. Further scalability of the design is currently under investigation via generation and CFD analysis of a geometrical scale-down model for viral clearance studies.